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Review article

The burden of influenza complications in different high-risk groups: a targeted literature review

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Keywords:
Influenza – Complications – High-risk – Hospitalization – Intensive care unit – Mechanical ventilation – Mortality

Abbreviations:
CASP, Critical Appraisals Skills Programme – COPD,chronic obstructive pulmonary disease – HIV, human immunodeficiency virus – ICU, intensive care unit – ILI, influenza-like illness – LCI, laboratory-confirmed influenza – LRTI, lower respiratory tract infection – US, United States

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Abstract

Objectives:
The objective was to review the published literature on seasonal influenza to assess the differences between complications and mortality rates for those adults at high risk of influenza complications, including the resource use of those hospitalized with influenza complications.

Methods:
A targeted literature review was performed using electronic database keyword searches, specific inclusion criteria, quality rating of the reviewed full-text articles and abstraction of data to present published evidence on the incidence, complication rates and health service use associated with clinical influenza in different adult high-risk groups including those who are aged 65 years and older or those with different chronic underlying medical conditions.

Results:
Key findings for incidence rates of clinical influenza were that incidence rates are similar among people with chronic cardiovascular or respiratory comorbidity, and may be higher in those with allogeneic stem cell transplants compared to those with autologous transplants. Rates of hospitalization and/or pneumonia or lower respiratory tract infection for those with chronic conditions or those who are immunocompromised are substantially higher than those in people over age 65 but without additional high-risk factors. A person who is hospitalized and has a laboratory-confirmed influenza diagnosis has a probability of intensive care unit admission of between 11.8–28.6% and of death of between 2.9–14.3%.

Conclusions:
These findings indicate that although the burden of influenza varied across high-risk groups, it also varied widely across studies within a single high-risk group. A key finding was that those over 65 years of age but without additional high-risk factors had a low risk of influenza complications. A limitation of the review is that most of the studies of hospitalized patients did not present outcomes data separately by high-risk group and only limited data were identified on rates of hospitalization or lower respiratory tract infection for most high-risk groups. Information about influenza complication rates and resource use, including influenza vaccines, chemoprophylaxis and/or treatment strategies for different high-risk groups, is needed to evaluate new interventions.

Background

Influenza is a seasonal disease with a northern hemisphere and a southern hemisphere winter epidemic pattern seeded in some seasons by influenza virus circulating in Southeast Asia[1]. Influenza has characteristic symptoms of sudden onset of high fever, aching muscles, headache, severe fatigue, non-productive cough, sore throat, and runny nose[2]. While most infected people recover within 1–2

weeks without requiring medical treatment, in the very young, the elderly, and those with other serious medical conditions, infection can lead to exacerbations of the underlying condition, as well as neurologic complications, pneumonia, and death[2–5].

The groups at high-risk for influenza complications are defined by age, chronic conditions, immune status and behavioural/occupational factors. Table 1 presents a listing of high-risk medical conditions for which influenza vaccination is recommended[6–8]. In addition to those recommended for vaccination, other groups that may have a high risk of complications include pre-term infants and all infants aged younger than 6 months[9] and hospitalized patients, especially those in intensive care units (ICUs)[10]. Persons with multiple risk factors, such as those aged over 65 years with a co-morbid condition, may be at especially high risk of complications[11].

Vaccination is generally considered to be the most effective method for preventing both cases and complications of influenza[12]. However, the vaccine coverage rates for the high-risk groups are generally not more than 50%, with the exception of those aged older than 65 years, who generally have vaccine coverage rates of at least 65%[7,13]. In addition, studies have shown that vaccination is less effective at promoting an immune response in the elderly and in those who are immunocompromised than in other groups[14–16]. A Cochrane systematic review of vaccination in the elderly concluded that the impact of vaccination on the rate of influenza complications could not be determined from the published literature[17]. A recently published systematic review of influenza vaccines in the US also concluded that evidence for protection in adults aged 65 years or older is lacking and protection by the vaccine for all groups is greatly reduced or absent in some seasons[18].

Table 1. People recommended for influenza vaccination because of high risk of complications.

High-risk group
By age
2–4 years
≥ 65 years
Chronic respiratory disease including asthma, COPD, and cystic fibrosis
Chronic heart disease including congestive heart failure and acute coronary syndromes
Chronic neurological disease including multiple sclerosis and Parkinson's disease
Chronic kidney or liver disease or hematologic disorders
Metabolic disorders including diabetes and morbid obesity
Immunocompromised individuals including post-transplant, HIV infection, during chemotherapy
Other
Pregnant women
People living in nursing homes

COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus.
Sources: United Kingdom[6]; US[7]; all countries[8].

Prophylaxis or treatment with antiviral drugs is also recommended for those at high risk of influenza complications. For example, in the US, antiviral prophylaxis or treatment with neuraminidase-inhibitors is recommended for those at high-risk of influenza complications[19]. Nevertheless, there are only limited data, mostly from observational studies, on the impact of the neuraminidase inhibitors zanamivir, oseltamivir, or peramivir on influenza complication rates or deaths in high-risk groups. Because of the lack of large randomized clinical trials among those at high risk, there is currently no consensus on the value of current antiviral therapies for reducing the influenza complication and mortality rates in high-risk groups[20,21].

Because of the controversy around the level of protection conferred by influenza vaccination and the value of current antiviral therapies for reducing complication and mortality rates in high-risk groups, an unmet need remains for new effective treatments and/or management strategies for influenza. However, this unmet need may differ for the high-risk group categories defined in Table 2. To better understand the unmet need in the different high-risk group categories, it is necessary to analyse the disease burden within each group separately. In this article, we present the results of a targeted literature review to evaluate for different high-risk groups the annual incidence rates for clinical influenza, clinical complication rates, and healthcare resource use. This information is of critical importance for the targeting of new therapies and prophylactic options as well as for their economic evaluation.

Methods

To characterize the burden of seasonal influenza complications in different high-risk adult groups, we followed the model of the disease progression shown in Figure 1. Prior to initiating the targeted literature review, the methodology to be used for the searches, screening process (inclusion and exclusion criteria), and data extraction were defined as follows: The search focused on data published since 1990 to October 2011 in the MEDLINE database (using the PubMed platform). In addition, a bibliographic reference list of full-text articles identified with the electronic MEDLINE searches was reviewed to identify any relevant articles.

We performed two sets of electronic searches of the MEDLINE database. The first set of searches used title keywords relating to outcomes associated with influenza complications and included the following keyword combinations:

- influenza*[ti] AND hospital*[ti] NOT (H1N1[ti] OR pandemic[ti] OR children[ti] OR pediatric[ti] OR infants[ti] OR workers[ti])

Table 2. Probability of a clinical case of influenza.

Age	Risk group (vaccination rate)	Annual influenza rate	Country	Years	Study quality			*n*	Reference
					Design	# Sites and population representative?*	Influenza defined		
65+	Otherwise healthy	2.4–5.0%	US	1999–2003	PC	Multiple; Cannot tell	LCI	608	Falsey *et al.*[25]
	Living in the community (0%)	6.55%	UK, NL	1991–1994	MA	Multiple; Cannot tell	LCI	1098	Turner *et al.*[5]
	Living in the community (58.9–64.3%)	0.23–1.52%	ES	2002–2005	PC	Multiple; Cannot tell	ILI	11,240	Vila-Córcoles *et al.*[24]
	Registered with general practitioner	0.99%	UK	1991–1996	GPRD	Multiple; Yes	ILI	507,556	Meier *et al.*[43]
	Living in residential care (very high)	4.85%	US, JA, UK, FR, EU	1985–1999	MA	Multiple; Cannot tell	LCI	18,566	Turner *et al.*[5]
All	CHF or CLD	2.4–7.2%	US	1999–2003	PC	Multiple; Cannot tell	LCI	540	Falsey *et al.*[25]
	SCT	0.9%	EU, AU	1997–1998	PC	Multiple; Yes	LCI	1973	Ljungman *et al.*[44]
	SCT, allogeneic	6.55%	ES	1999–2003	PC	Single; Yes	LCI	172	Martino *et al.*[26]
	SCT, autologous	3.05%	ES	1999–2003	PC	Single; Yes	LCI	240	Martino *et al.*[26]

*Was the population representative of the age, risk group, country and site(s) studied in the analysis?
AU, Australia; CHF, congestive heart failure; CLD, chronic lung disease; ES, Spain; EU, Europe; GPRD, General Practice Research Database; ILI, influenza-like illness; LCI, laboratory-confirmed influenza; MA, meta-analysis of clinical trial data; PC, prospective cohort; SCT, stem cell transplant; UK, United Kingdom; US, United States.

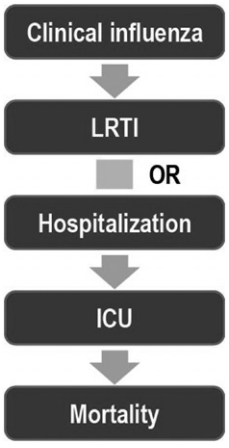

Figure 1. Framework for assessment of the burden of influenza complications. ICU, intensive care unit; LRTI, lower respiratory tract infection.

- influenza*[ti] AND (death[ti] or mortality[ti]) NOT (H1N1[ti] OR pandemic[ti] OR children[ti] OR pediatric[ti] OR infants[ti] OR workers[ti])
- influenza*[ti] AND pneumonia[ti] NOT (H1N1[ti] OR pandemic[ti] OR children[ti] OR pediatric[ti] OR infants[ti] OR workers[ti])
- influenza*[ti] AND outcome*[ti] NOT (H1N1[ti] OR pandemic[ti] OR children[ti] OR pediatric[ti] OR infants[ti] OR workers[ti])
- (influenza*[ti] OR 'respiratory virus'[ti] OR 'respiratory viruses'[ti]) AND prospective[ti] AND study[ti] NOT (H1N1[ti] OR pandemic[ti] OR children[ti] OR pediatric[ti] OR infants[ti] OR workers[ti])

The second set of searches included title searches for articles that included keywords for seasonal influenza and the following specific conditions in adults associated with a high risk for influenza complications: human immunodeficiency virus (HIV) infection, heart disease, renal disease, diabetes, multiple sclerosis, cystic fibrosis, stem cell or bone marrow transplant, solid organ transplant, asthma, chronic obstructive pulmonary disease (COPD), and the elderly.

The outcomes of interest in this review were (1) the annual incidence of clinical cases of seasonal influenza, (2) the probability of pneumonia or lower respiratory tract infection (LRTI) or hospitalization for those with a clinical case of influenza, (3) the probability of ICU admission and mechanical ventilation for those hospitalized with influenza, and (4) the probability of dying from influenza. In order to better understand the impact of seasonal influenza complications on medical resource use, other outcomes of interest included length of stay in the hospital and the ICU and duration on mechanical ventilation.

Titles and abstracts of the studies identified from the electronic database were screened, and full-text copies were obtained for those that appeared to present

quantitative data on one of the outcomes of interest for the review. Data were abstracted from English-language articles that presented quantitative information on at least one of the following topics for those with clinical influenza for at least one of the high-risk groups: clinical influenza attack rates, probability of hospitalization or pneumonia/LRTI or mortality, ICU admission and mechanical ventilation use, and/or length of stay at each level of care. The abstracted data were presented in a set of tables presenting the outcomes by specific high-risk groups.

For each study included in the tables, information related to the following study characteristics was included in the tables as indicators of study quality: study design (retrospective cohort or database, prospective cohort or other); the number of sites included in the study (single or multiple); study sample representative of the high-risk population studied at the site(s) (yes, cannot tell, and no); the method used to identify a case of influenza in the study (influenza or influenza-like illness [ILI] diagnosis, influenza diagnosis, laboratory-confirmed influenza [LCI]); and the extent to which the outcome was clearly defined (yes, cannot tell, no). These quality ratings were adapted from questions 2, 3, 4, and 5 of the CASP checklist for cohort studies[22]. These questions were considered of greatest relevance for our study objectives, and this approach is recommended for reviews of observational studies by the University of York Center for Reviews and Dissemination[23].

Results

We reviewed 1845 titles and abstracts, and 121 full-text articles. Of these, we selected 31 articles that presented quantitative data on influenza attack rates, complication rates, or resource use in high-risk groups. Of the selected articles, the majority were from the US (19), with three from Canada, two from Spain, two from France, one from Italy, one from the UK, and three using data from multiple countries. Fourteen of the studies were prospective cohort studies, 14 were retrospective cohort studies or database studies, and three used other methods, meta-analysis of clinical trial data, or estimation of the excess risk of hospitalization or death. Seventeen of the studies were multi-site studies, and 14 were single-site studies. Twenty-two of the studies estimated the complications associated with LCI, while the other nine studied those with an influenza or ILI diagnosis in the medical record that was not confirmed in the laboratory.

Table 2 presents a summary of studies that estimated the probability of individuals in different high-risk groups having a clinical case of influenza each year. The reviewed articles included many influenza seasons, from 1985–2003, and multiple countries. Data were limited and, in the articles reviewed, clinical influenza rates ranged from a low for ILI of 0.23% for those aged 65 years and older living in the community with a vaccination rate of 59–64% in Spain in 2002–2005[24] to a high for LCI of 7.2% among patients of all ages with congestive heart failure or chronic pulmonary disease in the US in the 2001–2002 influenza season[25]. The Vila-Córcoles *et al.*[24] study only captured cases of ILI which resulted in a physician visit, while the Falsey *et al.*[25] study captured all symptomatic cases, whether or not they resulted in a physician visit. The Falsey *et al.*[25] study, conducted over four influenza seasons, found that rates of confirmed clinical influenza in otherwise healthy elderly (2.4–5.0%) were similar to the rates in those of all ages with congestive heart failure or chronic pulmonary diseases (2.4–7.2%). In another study in Spain in 1999–2003 in stem cell transplant patients, those with an allogeneic transplant had a greater probability of clinical influenza (6.55%) than those with an autologous transplant (3.05%)[26].

Table 3 presents estimates of the probability of pneumonia or LRTI in high-risk groups by age and high-risk sub-group. The probability of pneumonia or LRTI in those with confirmed influenza ranged from 0% among those aged 65 or more years who were otherwise healthy and living in the community in the US in 1999–2003[25] to 80% among adults with leukemia in the US in 1993–1994[27]. The rates were considerably higher in studies that included only hospitalized patients with an influenza diagnosis or LCI (27–48%) or that studied patients with hematologic disorders, stem cell or bone marrow transplants, and solid organ transplants who were not treated with antiviral drugs (26–83%). Two retrospective influenza cohort studies of people with hematological malignancies or stem cell transplants or both compared rates of pneumonia and LRTI in those treated with antiviral drugs and those not treated with these drugs[28,29]. Both studies found lower rates of pneumonia or LRTI in those treated with antiviral drugs.

Table 4 presents estimates of the probability of hospitalization by age and high-risk sub-group. The probability of hospitalization given influenza ranged from 0% for those aged 65 years and older who were otherwise healthy and living in the community in the US in 1999–2003[25] to 20.8% among those with cancer or taking chronic corticosteroids with an influenza diagnosis in 1996–1997 in the US[30] or 20% in those with congestive heart failure or chronic lung disease with LCI in the US[25].

Estimates of the probability of ICU admission for those hospitalized with influenza are presented in Table 5. The probability of ICU admission was 4.2% for those aged 65 years or older with influenza as either a primary or secondary diagnosis code for influenza, but not necessarily with LCI, in France from a hospital database study in 2006–2007[31], and ranged between 11.4–28.6% for seven US and Canadian studies reviewed in people hospitalized with LCI.

Table 3. Probability of pneumonia or lower respiratory tract infection or chest infiltrates, given influenza.

Age	Risk group	Probability pneumonia or LRTI	Country	Years	Study quality				*n*	Reference
					Design	# Sites and population representative?*	Influenza defined	Outcome well defined		
65+	GP visit, NHS high risk	1.3%	UK	1991–1996	CrS using GPRD	Multiple; Yes	ILI	Yes	7407	Meier *et al.*[43]
	GP visit, NHS low risk	1.0%	UK	1991–1996	CrS using GPRD	Multiple; Yes	ILI	Yes	10145	Meier *et al.*[43]
	Healthy, community	0%	US	1999–2003	PC	Multiple; Can't tell	LCI	Yes	24	Falsey *et al.*[25]
All	CHF or CLD, community	10%	US	1999–2003	PC	Multiple; Can't tell	LCI	Yes	20	Falsey *et al.*[25]
	Diabetes, no AV	2.6%	US	2000–2006	CrS using CDB	Multiple; Can't tell	ID	Yes	6171	Orzeck *et al.*[45]
	Diabetes, AV-OS	2.1% (ns)	US	2000–2006	CrS using CDB	Multiple; Can't tell	ID	Yes	2919	Orzeck *et al.*[45]
	Hospitalized	27%	US	2002–2004	RC	Single; Yes	ID	Yes	207	Babcock *et al.*[33]
	Hospitalized	30%	US	1999–2003	PC	Single; Yes	LCI	Yes	144	Falsey *et al.*[25]
	High-risk hospitalized	52.3%	US	1999–2003	PC	Single; Yes	LCI	Yes	193	Murata *et al.*[46]
	Hospitalized	48.6%	US	1999–2000	PC	Single; Yes	LCI	Yes	35	Oliveira *et al.*[37]
	SCT, no AV	35%	US	1989–2009	RC	Single; Yes	LCI	Yes	58	Boudreault *et al.*[28]
	SCT, AV-RM, AM, OS, or ZN	4% ($p<0.01$)	US	1989–2009	RC	Single; Yes	LCI	Yes	84	Boudreault *et al.*[28]
	SCT	29%	US	1989–2002	RC	Single; No	LCI	Yes	62	Nichols *et al.*[47]
	SCT	44%	EU + AU	1997–2000	PC	Multiple; Yes	LCI	Yes	36	Ljungman *et al.*[44]
	SCT, autologous	26%	ES	1999–2003	PC	Single; Yes	LCI	Yes	15	Martino *et al.*[26]
	SCT, allogeneic	55%	ES	1999–2003	PC	Single; Yes	LCI	Yes	24	Martino *et al.*[26]
	BMT, hospitalized	66%	US	1991–1994	PC	Single; Yes	LCI	Yes	12	Whimbey *et al.*[48]
	BMT, hospitalized	75%	US	1991–1992	PC	Single; Yes	LCI	Yes	8	Whimby *et al.*[49]
	Leukemia	80%	US	1993–1994	PC	Single; Yes	LCI	Yes	15	Yousuf *et al.*[27]
	HM/SCT, no AV	42%	US	2000–2002	RC	Single; Yes	LCI	Yes	71	Chemaly *et al.*[29]
	HM/SCT, AV – OS, or RV	10% ($p<0.005$)	US	2000–2002	RC	Single; Yes	LCI	Yes	41	Chemaly *et al.*[29]
	SOT, hospitalized	42–83%	US	1990–2000	RC	Single; Yes	LCI	Yes	30	Vilchez *et al.*[50]
	IC, hospitalized	53%	FR	1998–2008	RC	Single; Yes	LCI	Yes	100	Schnell *et al.*[32]
	HIV infection	16.3%	US	1997–1999	RC	Single; Yes	LCI	Yes	43	Skiest *et al.*[41]

*Was the population representative of the age, risk group, country, and site(s) studied in the analysis?

AM, amantadine; AU, Australia; AV, antiviral drug therapy; BMT, bone marrow transplant; CDB, claims database; CHF, congestive heart failure; CLD, chronic lung disease; CrS, cross-sectional; ES, Spain; EU, Europe; FR, France; GP, general practitioner; GPRD, General Practice Research Database (UK); HIV, human immunodeficiency virus; HM, hematological malignancy; IC, immunocompromised; ID, influenza diagnosis; ILI, influenza like illness; JA, Japan; LCI, laboratory-confirmed influenza; LRTI, lower respiratory tract infection; NHS, National Health Service; NL, The Netherlands; PC, prospective cohort; OS, oseltamivir; RC, retrospective cohort; RM, rimantadine; RV, ribavirin; SCT, stem cell transplant; SOT, solid organ transplant; UK, United Kingdom; US, United States; ZN, zanamivir.

Table 4. Probability of hospitalization, given influenza.

Age	Risk group	Probability of hospital stay	Country	Years	Study quality				*n*	Reference
					Design	# Sites and population representative?*	Influenza defined	Outcome well defined		
65+	All risk levels	8.8%	US	1996–1997	CrS using CDB	Multiple; Yes	ID	Yes	170	Irwin *et al.*[30]
	Otherwise healthy	0%	US	1999–2003	PC	Multiple; Can't tell	LCI	Yes	24	Falsey *et al.*[25]
65–74	NHS high risk	2.4%	UK	1990–1997	CC for EH	Multiple; Yes	LCI	Yes	87,332	Turner *et al.*[5]
	NHS low risk	0.44%	UK	1990–1997	CC for EH	Multiple; Yes	LCI	Yes	181,381	Turner *et al.*[5]
75+	NHS high risk	4.08%	UK	1990–1997	CC for EH	Multiple; Yes	LCI	Yes	102,425	Turner *et al.*[5]
	NHS low risk	1.13%	UK	1990–1997	CC for EH	Multiple; Yes	LCI	Yes	141,444	Turner *et al.*[5]
All	High risk or 65+ no AV	3.2%	NH, SH	1997–2000	MA	Multiple; Yes	LCI	Yes	401	Kaiser *et al.*[51]
	High risk or 65+ AV-OS	1.6% ($p = 0.16$)	NH, SH	1997–2000	MA	Multiple; Yes	LCI	Yes	368	Kaiser *et al.*[51]
	Chronic corticosteroids	20.7%	US	1996–1997	CrS using CDB	Multiple; Yes	ID	Yes	29	Irwin *et al.*[30]
	Cancer	20.8%	US	1996–1997	CrS using CDB	Multiple; Yes	ID	Yes	72	Irwin *et al.*[30]
	CHD	17.2%	US	1996–1997	CrS using CDB	Multiple; Yes	ID	Yes	128	Irwin *et al.*[30]
	CLD	2.9%	US	1996–1997	CrS using CDB	Multiple; Yes	ID	Yes	1283	Irwin *et al.*[30]
	Diabetes	12.1%	US	1996–1997	CrS using CDB	Multiple; Yes	ID	Yes	116	Irwin *et al.*[30]
	CHF or CLD	20%	US	1999–2003	PC	Multiple; Can't tell	LCI	Yes	20	Falsey *et al.*[25]
	Asthma, COPD, diabetes or 65+	1.65%	IT	1998–1999	PC	Multiple; Can't tell	ID	Yes	1211	Sessa *et al.*[52]
	Diabetes, no AV	3.4%	US	2000–2006	CrS using CDB	Multiple; Can't tell	ID	Yes	6171	Orzeck *et al.*[45]
	Diabetes, AV - OS	2.0% ($p < 0.05$)	US	2000–2006	CrS using CDB	Multiple; Can't tell	ID	Yes	2919	Orzeck *et al.*[45]
	HIV infection	14.0%	US	1997–1999	RC	Single; Yes	LCI	Yes	43	Skiest *et al.*[41]

*Was the population representative of the age, risk group, country, and site(s) studied in the analysis?

AV, antiviral drug therapy; CBD, claims database; CC, case control; CHD, coronary heart disease; CHF, congestive heart failure; CLD, chronic lung disease; COPD, chronic obstructive pulmonary disease; CrS, cross-sectional; EH, excess hospitalizations; HIV, human immunodeficiency virus; ID, influenza diagnosis; IT, Italy; LCI, laboratory-confirmed influenza; MA, meta-analysis of clinical trials; NH, northern hemisphere countries; NHS, National Health Service; OS, oseltamivir; PC, prospective cohort; RC, retrospective cohort; SH, southern hemisphere countries; UK, United Kingdom; US, United States.

Table 5. Probability of intensive care unit admission given hospitalized for influenza.

Age	Risk group	Probability of intensive care	Country	Years	Study quality				*n*	Reference
					Design	# Sites and population representative?*	Influenza defined	Outcome well defined		
75+	All risk levels	11.4–17.1%	US	2005–2008	PC	Multiple; Yes	LCI	Yes	2050	Dao *et al.*[38]
50–74	All risk levels	14.7–20.4%	US	2005–2008	PC	Multiple; Yes	LCI	Yes	1738	Dao *et al.*[38]
65+	All risk levels	4.2%	FR	2006–2007	HDB	Multiple; Can't tell	ID	Can't tell	1346	Tomas *et al.*[31]
All	All risk levels	17.4%	US	2002–2004	RC	Single; Yes	LCI	Yes	207	Babcock *et al.*[33]
	All risk levels	12.9–16.8%	US	2005–2008	PC	Multiple; Yes	LCI	Yes	5055	Dao *et al.*[38]
	All risk levels	16.0%	CA	2005–2006	PC	Multiple; Yes	LCI	Yes	327	McGeer *et al.*[36]
	All risk levels	16.0%	CA	2005–2007	PC	Multiple; Yes	LCI	Yes	607	Muller *et al.*[39]
	All risk levels	11.8%	US	1999–2003	PC	Single; Yes	LCI	Yes	144	Falsey *et al.*[25]
	All risk levels	28.6%	US	1999–2000	PC	Single; Yes	LCI	Yes	35	Oliveira *et al.*[37]
	ARS	16.0%	US	1999–2003	PC	Single; Yes	LCI	Yes	101	Murata *et al.*[46]
	No ARS	13.0%	US	1999–2003	PC	Single; Yes	LCI	Yes	92	Murata *et al.*[46]

*Was the population representative of the age, risk group, country, and site(s) studied in the analysis?
ARS, acute respiratory symptoms; CA, Canada; FR, France; HDB, hospital database; ID, influenza diagnosis; LCI, laboratory-confirmed influenza; PC, prospective cohort; RC, retrospective cohort; US, United States.

Estimates of the probability of mechanical ventilation given hospital or ICU admission by age and high-risk sub-group are presented in Table 6. The probability of mechanical ventilation for those with LCI ranged from 0% among immunocompromised patients of all ages admitted to the hospital without a pneumonia diagnosis in France in 1998–2008[32] to 21.0% for those with a pneumonia diagnosis[32]. The probability of mechanical ventilation for patients admitted to the ICU ranged from 69–78% in the US[33,34]. In other studies of all hospital admissions, the probability of mechanical ventilation ranged between 3.8% for those aged 65 years and over with cancer and an influenza diagnosis[35] to 26% of those with COPD and LCI[33].

Estimates of the probability of death at the time of an influenza episode from all causes by age and high-risk sub-group are shown in Table 7. The estimates of death rates in hospitalized patients from the French hospital database study that included those with a primary or secondary diagnosis code for influenza, but not necessarily with LCI[31], were lower (0.3% for those aged 5–64 years and 3.1% for those aged 65 years and over) than estimates in studies that estimated the death rates for those hospitalized with LCI (2.9–14.3% for all ages and 13.5% for those aged 65 years and over) in US and Canadian studies[25,33,36–39] and in those with an influenza diagnosis and cancer (8.3% for those aged 18–64 years and 9.5% for those with cancer aged 65 years and over)[35]. The estimated probability of death in those with stem cell and other transplants ranged from 4–9% in those treated with antiviral therapy and from 17–27% for those not treated with antiviral therapy[28,29]. However, these estimates were for all-cause death and included deaths associated with the underlying disease. The estimated death rates for those admitted to the ICU depended on the high-risk group analysed and ranged from 13.6% for those with hypertension to 52.4% for immunocompromised patients in a multi-site US study[34].

Finally, estimates of the length of stay in the hospital and ICU and the duration on mechanical ventilation for those using these hospital resources, by age and high-risk sub-group, are presented in Table 8. Some of the studies reviewed presented mean total length of stay, and some presented the median length of stay. Four studies presented both values[30,31,40,41], and all four showed that the mean length of stay was longer than the median length of stay by between 1.2–5 days. Two studies estimated a longer length of stay for those with pneumonia or other poor outcomes than for those with less serious symptoms[32,42]. The two studies that estimated length of stay for those admitted to the ICU did not find a longer total length of stay in the hospital than the estimates for those admitted to the hospital[34,36]. There did not seem to be a clear pattern for different hospital resource use by country. Length of stay in the ICU and duration on mechanical ventilation varied considerably between studies.

Discussion

The articles identified in the literature review found only limited data available to differentiate between high-risk groups in rates of influenza infection and associated complication rates and resource use. In addition, estimates of complication rates or resource use from different studies in the same high-risk group varied substantially. Estimates of

Table 6. Probability of mechanical ventilation given intensive care unit or hospital admission for influenza.

Age	Risk group	Probability mechanical ventilation	Country	Years	Study quality				*n*	Reference
					Design	# Sites and population representative?*	Influenza defined	Outcome well defined		
65+	Hospital admits, cancer	3.8%	US	1998–2001	CrS using HDB	Multiple; Can't tell	ID	Yes	49,611	Cooksley *et al.*[35]
18–64	Hospital admits, cancer	5.8%	US	1998–2001	CrS using HDB	Multiple; Can't tell	ID	Yes	13,532	Cooksley *et al.*[35]
All	Hospital admits	9.8%	US	1998–1999	RC	Single; Yes	LCI	Yes	132	Angelo *et al.*[42]
	Hospital admits	12.1%	US	2002–2004	RC	Single; Yes	LCI	Yes	207	Babcock *et al.*[33]
	Hospital admits	9.0%	CA	2005–2007	PC	Multiple; Yes	LCI	Yes	607	Muller *et al.*[39]
	Hospital admits	10.4%	US	1999–2003	PC	Single; Yes	LCI	Yes	144	Falsey *et al.*[25]
	Hospital admits, COPD	26.0%	US	2002–2004	RC	Single; Yes	LCI	Yes	46	Babcock *et al.*[33]
	Hospital admits, no COPD	8.0%	US	2002–2004	RC	Single; Yes	LCI	Yes	161	Babcock *et al.*[33]
	Hospital admits, ARS	10.0%	US	1999–2003	PC	Single; Yes	LCI	Yes	101	Murata *et al.*[46]
	Hospital admits, no ARS	12.0%	US	1999–2003	PC	Single; Yes	LCI	Yes	92	Murata *et al.*[46]
	Hospital admits, SCT	9.1%	US	1989–2009	RC	Single; Yes	LCI	Yes	142	Boudreault *et al.*[28]
	Hospital admits, SCT, no AV	12.0%	US	1989–2009	RC	Single; Yes	LCI	Yes	58	Boudreault *et al.*[28]
	Hospital admits, SCT, AV-RM, AM, OS, or ZN	4.0% ($p = 0.25$)	US	1989–2009	RC	Single; Yes	LCI	Yes	84	Boudreault *et al.*[28]
	Hospital admits, IC, PN	21.0%	FR	1998–2008	RC	Single; Yes	LCI	Yes	53	Schnell *et al.*[32]
	Hospital admits, IC, no PN	0%	FR	1998–2008	RC	Single; Yes	LCI	Yes	47	Schnell *et al.*[32]
	Intensive care unit admits	69.4%	US	2002–2004	RC	Single; Yes	LCI	Yes	36	Babcock *et al.*[33]
	Intensive care unit admits	78.4%	US	1999–2006	RC	Multiple; Yes	LCI	Yes	111	Li *et al.*[34]

* Was the population representative of the age, risk group, country, and site(s) studied in the analysis?

AM, amantadine; ARS, acute respiratory symptoms; AV, antiviral drug therapy; CA, Canada; COPD, chronic obstructive pulmonary disease; CrS, cross-sectional; FR, France; HDB, hospital database; IC, immunocompromised; ID, influenza diagnosis; LCI, laboratory-confirmed influenza; OS, oseltamivir; PC, prospective cohort; PN, pneumonia; RC, retrospective cohort; RM, rimantadine; SCT, stem cell transplant; US, United States; ZN, zanamivir.

Table 7. Probability of death with influenza episode.

Age	Risk group	Probability death	Country	Years	Study type				*n*	Reference
					Design	# Sites and population representative?*	Influenza defined	Outcome well defined		
65+	GP visit, NHS high risk	1.5%	UK	1991–1996	CrS using GPRD	Multiple; Yes	ILI	Yes	7407	Meier *et al.*[43]
	GP visit, NHS low risk	1.1%	UK	1991–1996	CrS using GPRD	Multiple; Yes	ILI	Yes	10,145	Meier *et al.*[43]
	Hospital admits	13.5%	CA	2005–2007	PC	Multiple; Yes	LCI	Yes	451	Muller *et al.*[39]
	Hospital admits	3.1%	FR	2006–2007	CrS using HDB	Multiple; Can't tell	ID	Yes	1346	Tomas *et al.*[31]
	Hospital admits, cancer	9.5%	US	1998–2001	CrS using HDB	Multiple; Can't tell	ID	Yes	49,611	Cooksley *et al.*[35]
18–64	Hospital admits, cancer	8.3%	US	1998–2001	CrS using HDB	Multiple; Can't tell	ID	Yes	13,532	Cooksley *et al.*[35]
5–64	Hospital admits	0.3%	FR	2006–2007	CrS using HDB	Multiple; Can't tell	ID	Yes	3258	Tomas *et al.*[31]
15–49	GP visit, NHS high risk	0.04%	UK	1991–1996	CrS using GPRD	Multiple; Yes	ILI	Yes	12,195	Meier *et al.*[43]
50–64	GP visit, NHS high risk	0.20%	UK	1991–1996	CrS using GPRD	Multiple; Yes	ILI	Yes	5402	Meier *et al.*[43]
All	Hospital admits	11.7%	CA	2005–2007	PC	Multiple; Yes	LCI	Yes	607	Muller *et al.*[39]
	Hospital admits	3.4%	US	2002–2004	RC	Single; Yes	LCI	Yes	207	Babcock *et al.*[33]
	Hospital admits	2.9–4.4%	US	2005–2008	PC	Multiple; Yes	LCI	Yes	5055	Dao *et al.*[38]
	Hospital admits	8.3%	CA	2005–2006	PC	Multiple; Yes	LCI	Yes	327	McGeer *et al.*[36]
	Hospital admits	7.0%	US	1999–2003	PC	Single; Yes	LCI	Yes	144	Falsey *et al.*[25]
	Hospital admits	14.3%	US	1999–2000	PC	Single; Yes	LCI	Yes	35	Oliveira *et al.*[37]
	Hospital admits, high risk	12.3%	CA	2005–2007	PC	Multiple; Yes	LCI	Yes	568	Muller *et al.*[39]
	Hospital admits, CLD	12.1%	CA	2005–2007	PC	Multiple; Yes	LCI	Yes	257	Muller *et al.*[39]
	Hospital admits, CHD	14.2%	CA	2005–2007	PC	Multiple; Yes	LCI	Yes	360	Muller *et al.*[39]
	Hospital admits, IC and Diabetes	13.2%	CA	2005–2007	PC	Multiple; Yes	LCI	Yes	372	Muller *et al.*[39]
	Hospital admits, NMD	29.8%	CA	2005–2007	PC	Multiple; Yes	LCI	Yes	47	Muller *et al.*[39]
	Hospital admits, ARS	5.9%	US	1999–2003	PC	Single; Yes	LCI	Yes	101	Murata *et al.*[46]
	Hospital admits, no ARS	5.4%	US	1999–2003	PC	Single; Yes	LCI	Yes	92	Murata *et al.*[46]
	SCT	12.0%	US	1989–2009	RC	Single; Yes	LCI	Yes	143	Boudreault *et al.*[28]
	SCT, no AV	17.0%	US	1989–2009	RC	Single; Yes	LCI	Yes	58	Boudreault *et al.*[28]
	SCT, AV – RM, AM, OS, or ZN	4.0% ($p = 0.05$)	US	1989–2009	RC	Single; Yes	LCI	Yes	84	Boudreault *et al.*[28]
	SCT,MV	69.0%	US	1989–2009	RC	Single; Yes	LCI	Yes	13	Boudreault *et al.*[28]
	SCT	23.0%	EU + AU	1997–2000	PC	Multiple; Yes	LCI	Yes	1973	Ljungman *et al.*[44]
	SCT, autologous	0%	ES	1999–2003	PC	Single; Yes	LCI	Yes	15	Martino *et al.*[26]
	SCT, allogeneic	12.5%	ES	1999–2003	PC	Single; Yes	LCI	Yes	24	Martino *et al.*[26]
	SCT	10.0%	US	1989–2002	RC	Single; No	LCI	Yes	62	Nichols *et al.*[47]
	SCT, PN	28.0%	US	1989–2002	RC	Single; No	LCI	Yes	18	Nichols *et al.*[47]
	Hospital admits, BMT, PN	50.0%	US	1992–1994	PC	Single; Yes	LCI	Yes	8	Whimbey *et al.*[48]
	HM or SCT, no AV	27.0%	US	2000–2002	RC	Single; Yes	LCI	Yes	71	Chemaly *et al.*[29]
	HM or SCT, AV – OS, RV	9.0% ($p = 0.02$)	US	2000–2002	RC	Single; Yes	LCI	Yes	41	Chemaly *et al.*[29]
	HM	7.7%	ES	1999–2001	PC	Single; Yes	LCI	Yes	56	Martino *et al.*[53]
	Hospital admits, leukemia, PN	33.0%	US	1993–1994	PC	Single; Yes	LCI	Yes	12	Yousuf *et al.*[27]
	IC, PN	19.0%	FR	1998–2008	RC	Single; Yes	LCI	Yes	53	Schnell *et al.*[32]
	IC, no PN	0%	FR	1998–2008	RC	Single; Yes	LCI	Yes	47	Schnell *et al.*[32]
	ICU admits	18.9%	US	1999–2006	RC	Multiple; Yes	LCI	Yes	111	Li *et al.*[34]
	ICU admits, COPD	16.4%	US	1999–2006	RC	Multiple; Yes	LCI	Yes	55	Li *et al.*[34]
	ICU admits, CAD	13.9%	US	1999–2006	RC	Multiple; Yes	LCI	Yes	36	Li *et al.*[34]
	ICU admits, diabetes	13.9%	US	1999–2006	RC	Multiple; Yes	LCI	Yes	36	Li *et al.*[34]
	ICU admits, hypertension	19.6%	US	1999–2006	RC	Multiple; Yes	LCI	Yes	56	Li *et al.*[34]
	ICU admits, hypothyroidism	13.6%	US	1999–2006	RC	Multiple; Yes	LCI	Yes	22	Li *et al.*[34]
	ICU admits, IC	52.4%	US	1999–2006	RC	Multiple; Yes	LCI	Yes	21	Li *et al.*[34]
	ICU admits, Transplant	28.6%	US	1999–2006	RC	Multiple; Yes	LCI	Yes	7	Li *et al.*[34]

*Was the population representative of the age, risk group, country, and site(s) studied in the analysis?

ARS, acute respiratory symptoms; AU, Australia; AV, antiviral therapy; BMT, bone marrow transplant; CA, Canada; CAD, coronary artery disease; CHD, chronic heart disease; CLD, chronic lung disease; COPD, chronic obstructive pulmonary disease; CrS, cross-sectional; ES, Spain; EU, Europe; FR, France; GP, general practitioner; GPRD, General Practice Research Database; HDB, hospital database; HM, hematologic malignancy; IC, immunocompromised; ICU, intensive care unit; ID, influenza diagnosis; ILI, influenza-like illness; LCI, laboratory-confirmed influenza; MV, mechanical ventilation; NHS, National Health Service; NMD, neuromuscular disease; OS, oseltamivir; PC, prospective cohort; PN, pneumonia; RC, retrospective cohort; RV, ribavirin; SCT, stem cell transplant; UK, United Kingdom; US, United States.

Table 8. Length of stay in hospital, in intensive care unit, or on mechanical ventilation.

Age	Type of care, risk group	Length of stay (days)	Country	Years	Study quality				*n*	Reference
					Design	# Sites and population representative?*	Influenza defined	Outcome well defined		
Length of total hospital stay										
65+	Hospital admits	M, 9.1; MD, 7; SD, 12.3	FR	2006–2007	CrS using HDB	Multiple; Can't tell	ID	Yes	1346	Tomas *et al.*[31]
50+	Hospital admits,	M, 10.5–10.8; MD, 7–8	US	1979–2001	CC for EH	Multiple; Yes	ICD-9-CM 480-487	Yes	n/a	Thompson *et al.*[40]
50+	Hospital admits,	M, 7.8–8.6; MD, 5–6	US	1979–2001	CC for EH	Multiple; Yes	ICD-9-CM 390-519	Yes	n/a	Thompson *et al.*[40]
5–49	Hospital admits,	M, 7.5; MD, 5	US	1979–2001	CC for EH	Multiple; Yes	ICD-9-CM 480-487	Yes	n/a	Thompson *et al.*[40]
5–49	Hospital admits,	M, 5.8; MD, 3	US	1979–2001	CC for EH	Multiple; Yes	ICD-9-CM 390-519	Yes	n/a	Thompson *et al.*[40]
5–64	Hospital admits	M, 3.2; MD, 2; SD, 5.6	FR	2006–2007	CrS using HDB	Multiple; Can't tell	ID	Yes	5451	Tomas *et al.*[31]
All	Hospital admits, all	M, 7.4	US	1998–1999	RC	Single; Yes	LCI	Yes	132	Angelo *et al.*[42]
	Hospital admits	MD, 3–4; IQR, 2–6	US	2005–2008	PC	Multiple; Yes	LCI	Yes	5055	Dao *et al.*[38]
	Hospital admits	M, 8; SD, 5	US	1999–2003	PC	Single; Yes	LCI	Yes	144	Falsey *et al.*[25]
	Hospital admits	MD, 6; range, 1–103	CA	2005–2006	PC	Multiple; Yes	LCI	Yes	327	McGeer *et al.*[36]
	Hospital admits	M, 8.4; MD, 5	US	1996–1997	CrS using CDB	Multiple; Yes	LCI	Yes	103	Irwin *et al.*[30]
	Hospital admits, poor outcomes	M, 12.5	US	1998–1999	RC	Single; Yes	LCI	Yes	27	Angelo *et al.*[42]
	Hospital admits, good outcomes	M, 6.1	US	1998–1999	RC	Single; Yes	LCI	Yes	105	Angelo *et al.*[42]
	Hospital admits, ARS	M, 8.6; SD, 5.1	US	1999–2003	PC	Single; Yes	LCI	Yes	101	Murata *et al.*[46]
	Hospital admits, no ARS	M, 8.9 SD, 10	US	1999–2003	PC	Single; Yes	LCI	Yes	92	Murata *et al.*[46]
	Hospital admits, IC, PN	MD, 13; IQR, 6–23	FR	1998–2008	RC	Single; Yes	LCI	Yes	53	Schnell *et al.*[32]
	Hospital admits, IC, no PN	MD, 5; IQR, 1–8	FR	1998–2008	RC	Single; Yes	LCI	Yes	47	Schnell *et al.*[32]
	Hospital admits, HIV	M, 12; MD, 7; range, 2–30	US	1997–1999	RC	Single; Yes	LCI	Yes	6	Skiest *et al.*[41]
	Hospital admits, cancer	M, 6.1	US	1998–2001	CrS using HDB	Multiple; Can't tell	ID	Yes	64,008	Cooksley *et al.*[35]
	ICU admits	MD, 9.2; IQR, 5.7–15.0	US	1999–2006	RC	Multiple; Yes	LCI	Yes	111	Li *et al.*[34]
	ICU admits	MD, 6; range, 1–103	CA	2005–2006	PC	Multiple; Yes	LCI	Yes	52	McGeer *et al.*[36]
Length of stay in intensive care unit										
All	ICU admits	MD, 4; range, 1–64	US	2002–2004	RC	Single; Yes	LCI	Yes	36	Babcock *et al.*[33]
	ICU admits	MD, 3.0; IQR, 1.3–6.5	US	1999–2006	RC	Multiple; Yes	LCI	Yes	111	Li *et al.*[34]
	ICU admits	MD, 5; range, 1–22	CA	2005–2006	PC	Multiple; Yes	LCI	Yes	52	McGeer *et al.*[36]
	ICU admits	M, 28; SD, 260	US	1999–2000	PC	Single; Yes	LCI	Yes	10	Oliveira *et al.*[37]
	ICU admits	MD, 6; range, 4–14	CA	2005–2007	PC	Multiple; Yes	LCI	Yes	97	Muller *et al.*[39]
Duration of mechanical ventilation										
All	ICU admits	MD, 4; range, 1–60	US	2002–2004	RC	Single; Yes	LCI	Yes	36	Babcock *et al.*[33]
	ICU admits	MD, 3.0; IQR, 2.0–6.8	US	1999–2006	RC	Multiple; Yes	LCI	Yes	87	Li *et al.*[34]
	ICU admits	M, 21.5; SD, 20.5	US	1999–2000	PC	Single; Yes	LCI	Yes	10	Oliveira *et al.*[37]
	ICU admits	MD, 5; range, 2–13	CA	2005–2007	PC	Multiple; Yes	LCI	Yes	55	Muller *et al.*[39]
	ICU admits	MD, 7; range, 1–22	US	1989–2009	RC	Single; Yes	LCI	Yes	13	Boudreault *et al.*[28]

*Was the population representative of the age, risk group, country, and site(s) studied in the analysis?

ARS, acute respiratory symptoms; CC, case control; CA, Canada; CDB, claims database; CrS, cross-sectional; EH, excess hospitalizations; FR, France; HDB, hospital database; HIV, human immunodeficiency virus; IC, immunocompromised; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification (code); ICU, intensive care unit; ID, influenza diagnosis; IQR, interquartile range; LCI, laboratory-confirmed influenza; M, mean; MD, median; PC, prospective cohort; PN, pneumonia; RC, retrospective cohort; SD, standard deviation; US, United States.

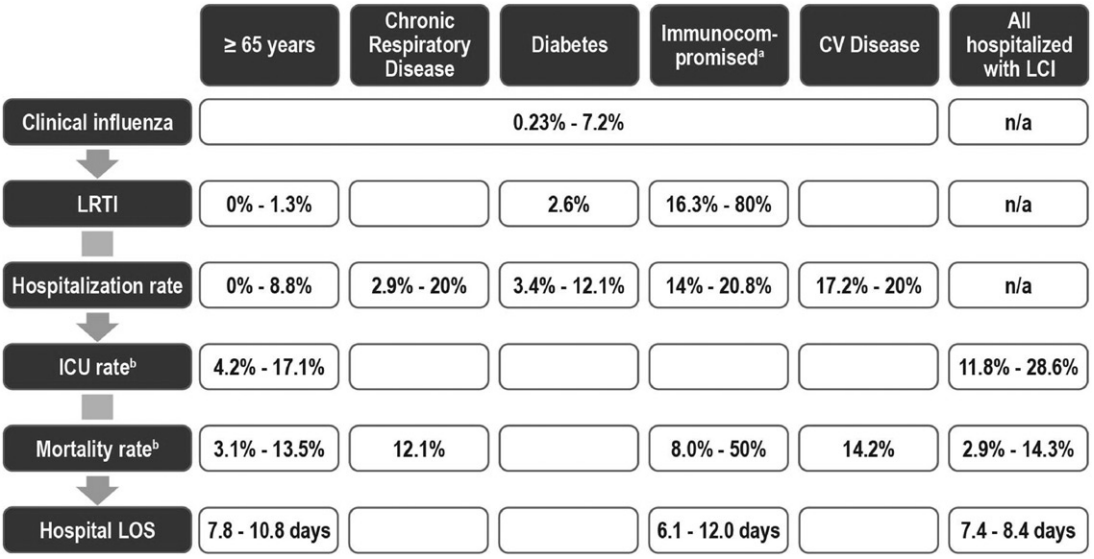

Figure 2. Overview of clinical outcomes and resource-use data associated with influenza complications by high-risk group. CV, cardiovascular; HIV, human immunodeficiency virus; ICU, intensive care unit; LCI, laboratory-confirmed influenza; LOS, length of stay; LRTI, lower respiratory tract infection. [a] Including those with HIV infection, post-transplant, and with cancer. [b] Rate for those hospitalized with a confirmed influenza diagnosis.

complications or resource use also varied according to whether the study included all those with an influenza diagnosis or influenza-like illness or included only those with LCI.

The framework displayed in Figure 1 for the presentation of the data postulated a clinical case of influenza that might (1) prompt a visit to the doctor or hospital emergency room, (2) include symptoms of LRTI such as pneumonia, (3) require inpatient hospital treatment both in regular and intensive care for influenza complications or exacerbations of an underlying chronic condition, (4) require respiratory support with mechanical ventilation, and (5) end in death. The probability of clinical influenza that prompts a visit to a physician or hospital is impacted by many factors other than the type of high-risk factor, including healthcare-seeking behaviour, the presence of co-morbidity, the dominant virus strain in the influenza season, the magnitude of the influenza epidemic, vaccination status, and the match of the vaccine with the circulating viruses. The outcome of clinical influenza infection is also dependent on the type of care received, including antiviral treatment. All of these factors are likely to vary by influenza season and country.

Figure 2 presents an overview of the data abstracted from the published studies where outcomes and resource use were presented for specific high-risk groups. It shows wide ranges for each estimate, with only limited data available for some high-risk groups, including those with chronic respiratory disease. When the data are viewed for individual categories of high-risk patients, there are some differences between the different groups. Many studies reviewed did not differentiate between high-risk groups, presenting, for example, estimates of outcomes for all people hospitalized with either an influenza diagnosis or with LCI.

We identified several studies that estimated the probability of a clinical case of influenza and its complications and resource use for those aged 65 years and older. However, the estimates, shown in Figure 2, show a wide range in the estimates for all elements of the burden of influenza, including hospitalization and death rates. Part of this range may be attributable to the grouping in many of these studies of those with or without a condition that puts them at higher risk of influenza complications. Thus, the Falsey *et al.*[25] prospective cohort study, which subdivided those aged 65 years and older into those with and without chronic conditions, found a large difference in rates of pneumonia and hospitalization between the two groups, although clinical influenza attack rates were similar in the two groups. Thus, in viewing the burden of complications in those aged 65 years and older, it is important to differentiate between those with and without underlying chronic medical conditions.

Although chronic respiratory disease is generally known to place a person at increased risk of influenza complication, there are only limited data that estimate the burden of influenza for this important high-risk group. Similarly for those with diabetes, although there are estimates of their risk of LRTI or hospitalization, no data were identified estimating the outcomes in this high-risk group once hospitalized. Mortality rates for those hospitalized with cardiovascular disease were similar to those with

chronic respiratory disease and those aged 65 years and older, but hospitalization rates were higher.

In contrast, several studies were identified among immunocompromised patients, defined as including those who are post-transplant, those with HIV infection, and those with cancer. All of these studies indicated that this high-risk group had higher rates of LRTI or hospitalization and higher mortality rates for those hospitalized. The mortality rates presented in Figure 2 are for all causes, including the underlying condition, but in those studies of the immunocompromised where the influenza mortality rate was presented separately, influenza mortality rates were also higher than in the other high-risk groups. In the immunocompromised groups, there were also some small observational studies that indicated that the risk of complications was lower when the influenza was treated with antiviral drugs[28,29].

Although the very young are recognized as one of the high-risk groups, data are lacking on what, besides age, puts them at risk for hospitalizations due to influenza complications. Furthermore, with the recent 2009 influenza A H1N1 pandemic and the replacement of the previous influenza A seasonal H1N1 strain with the pandemic strain as the new seasonal strain, it is becoming evident that younger people are experiencing influenza-related complications requiring hospitalization at a higher rate than in the past, when infected with 2009 influenza A H1N1. In only 50% of the children hospitalized with influenza, but in 87% of the adults, an underlying chronic medical condition putting them at high risk for complications was identified[54].

As a limitation, the targeted literature review only included title keyword searches of the MEDLINE database and only reviewed articles published in English. The Embase databases were not searched. The keyword searches were supplemented by hand searches of the bibliographies from the full-text papers reviewed. This review was intended to provide a general overview of existing data on the burden on influenza disease among widely accepted high-risk conditions and, as such, has identified what appear to be gaps in the literature presenting information on complication rates and resource use for different high-risk groups. In particular, studies specifically designed to differentiate between influenza complication rates in different high-risk categories would provide valuable information for assessing the value of new management strategies in the different high-risk groups. In addition, it should be recognized that conclusions drawn from studies in different risk groups will always be complicated by the seasonal variability and unpredictability of the influenza epidemic each year and by differences across countries and regions in the access to healthcare, the vaccination rate, and the structure of the healthcare system.

Conclusions

The articles included in this review provide information indicating that different high-risk groups might have different levels of risk from a clinical case of influenza. Thus, persons 65 years of age living in the community with no other high-risk conditions may have the lowest burden of influenza complications; among those with other high-risk conditions, a middle-aged person with diabetes who is immunocompetent may be at a lower risk for influenza complications than someone who is immunocompromised, regardless of age; and a person with a high-risk condition who has LCI and is admitted to the hospital with pneumonia/LRTI has a high likelihood of ICU admission, mechanical ventilation, and death. However, there was a wide range of estimates from studies of patients with the same high-risk condition. These findings can be used to evaluate new therapies, including better influenza vaccines, prophylaxis, and/or treatments strategies for different high-risk groups.

Transparency

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Declaration of financial/other relationships

JM has disclosed that she has received funding from Janssen to perform the literature review and to prepare this paper. She performs similar projects for many other pharmaceutical companies. MK, SL, and GH-T have disclosed that they are employed by Janssen, which is developing a compound for the treatment of influenza in high-risk groups.

Authors' contributions

MK, SL, and JM designed the literature review study, and JM performed the literature review. MK, GH-T, and JM jointly developed the outline for the paper, interpreted the results of the literature review, and wrote sections of the paper. All authors reviewed drafts of the paper and reviewed and approved the final paper.

References

1. Enserink M. Virology. Mapmaker for the world of influenza. Science 2008;320:310-11
2. World Health Organization (WHO). Acute Respiratory Infections (Update September 2009). Available at http://www.who.int/vaccine_research/diseases/ari/en/index1.html. [Last accessed 28 November 2012]
3. Rothberg MB, Haessler SD, Brown RB. Complications of viral influenza. Am J Med 2008;121:258-64
4. Rothberg MB, Haessler SD. Complications of seasonal and pandemic influenza. Crit Care Med 2010;38(Suppl 4):e91-7
5. Turner D, Wailoo A, Nicholson K, et al. Systematic review and economic decision modelling for the prevention and treatment of influenza A and B. Health Technol Assess 2003;7:iii-iv, xi–xiii, 1–170

6. Begum F, Pebody R. Seasonal influenza vaccine uptake among those 65 years and over and under 65 years at risk in England: Winter Season 2009-2010. London: Health Protection Agency, Department of Health; 2010. Available at http://www.dh.gov.uk/en/Publichealth/Immunisation/Keyvaccineinformation/DH_104070. [Last accessed 28 November 2012]
7. Fiore AE, Uyeki TM, Broder K, et al; Centers for Disease Control and Prevention (CDC). Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. MMWR Recomm Rep 2010;59:1-62
8. World Health Organization (WHO), Regional Office for Europe: WHO/Europe recommendations on influenza vaccination during the 2010/2011 Winter Season. 2011. Available at http://www.euro.who.int/__data/assets/pdf_file/0004/128839/Euro_flu_2010-2011.pdf. [Last accessed 28 November 2012]
9. van den Berg JP, Westerbeek EA, van der Klis FR, et al. Transplacental transport of IgG antibodies to preterm infants: a review of the literature. Early Hum Dev 2011;87:67-72
10. Salgado CD, Giannetta ET, Hayden FG, et al. Preventing nosocomial influenza by improving the vaccine acceptance rate of clinicians. Infect Control Hosp Epidemiol 2004;25:923-8
11. Nichol KL, Wuorenma J, von Sternberg T. Benefits of influenza vaccination for low-, intermediate-, and high-risk senior citizens. Arch Intern Med 1998;158:1769-76
12. Spaude KA, Abrutyn E, Kirchner C, et al. Influenza vaccination and risk of mortality among adults hospitalized with community-acquired pneumonia. Arch Intern Med 2007;167:53-9
13. Blank PR, Schwenkglenks M, Szucs TD. Vaccination coverage rates in eleven European countries during two consecutive influenza seasons. J Infect 2009;58:446-58
14. Goodwin K, Viboud C, Simonsen L. Antibody response to influenza vaccination in the elderly: a quantitative review. Vaccine 2006;24:1159-69
15. Goossen GM, Kremer LCM, van de Wetering MD. Influenza vaccination in children being treated with chemotherapy for cancer. Cochrane Database Syst Rev 2009;2:CD006484
16. Kunisaki KM, Janoff EN. Influenza in immunosuppressed populations: a review of infection frequency, morbidity, mortality, and vaccine responses. Lancet Infect Dis 2009;9:493-504
17. Jefferson T, Di Pietrantoni C, Al-Ansary LA, et al. Vaccines for preventing influenza in the elderly. Cochrane Database Syst Rev 2010;2:CD004876
18. Osterholm MT, Kelley NS, Sommer A, et al. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. Lancet Infect Dis 2012;12:36-44
19. Fiore AE, Fry A, Shay D, et al; Centers for Disease Control and Prevention (CDC). Antiviral agents for the treatment and chemoprophylaxis of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2011;60:1-25
20. Hernan MA, Lipsitch M. Oseltamivir and risk of lower respiratory tract complications in patients with flu symptoms: a meta-analysis of eleven randomized clinical trials. Clin Infect Dis 2011;53:277-9
21. Jefferson T, Jones M, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults: systematic review and meta-analysis. BMJ 2009;339:b5106
22. Critical Appraisal Skills Programme (CASP). Making sense of evidence about clinical effectiveness: 12 questions to help you make sense of cohort study, 2010. Available at http://www.casp-uk.net/wp-content/uploads/2011/11/CASP_Cohort_Appraisal_Checklist_14oct10.pdf. [Last accessed 28 November 2012]
23. Center for Reviews and Dissemination. Systematic Reviews: CRD's guidance for undertaking reviews in health care. York, UK: York Publishing Services, Ltd, 2008
24. Vila-Córcoles A, Rodriguez T, de Diego C, et al; EPIVAC Study Group. Effect of influenza vaccine status on winter mortality in Spanish community-dwelling elderly people during 2002-2005 influenza periods. Vaccine 2007;25:6699-707
25. Falsey AR, Hennessey PA, Formica MA, et al. Respiratory syncytial virus infection in elderly and high-risk adults. N Engl J Med 2005;352:1749-59
26. Martino R, Porras RP, Rabella N, et al. Prospective study of the incidence, clinical features, and outcome of symptomatic upper and lower respiratory tract infections by respiratory viruses in adult recipients of hematopoietic stem cell transplants for hematologic malignancies. Biol Blood Marrow Transplant 2005;11:781-96
27. Yousuf HM, Englund J, Couch R, et al. Influenza among hospitalized adults with leukemia. Clin Infect Dis 1997;24:1095-9
28. Boudreault AA, Xie H, Leisenring W, et al. Impact of corticosteroid treatment and antiviral therapy on clinical outcomes in hematopoietic cell transplant patients infected with influenza virus. Biol Blood Marrow Transplant 2011;17:979-86
29. Chemaly RF, Ghosh S, Bodey GP, et al. Respiratory viral infections in adults with hematologic malignancies and human stem cell transplantation recipients: a retrospective study at a major cancer center. Medicine (Baltimore) 2006;85:278-87
30. Irwin DE, Weatherby LB, Huang WY, et al. Impact of patient characteristics on the risk of influenza/ILI-related complications. BMC Health Serv Res 2001;1:8
31. Tomas J, Lelièvre F, Bercelli P, et al. Hospital admissions related to influenza in France during the 2006/2007 epidemic. Rev Epidemiol Sante Publique 2011;59:159-67
32. Schnell D, Mayaux J, de Bazelaire C, et al. Risk factors for pneumonia in immunocompromised patients with influenza. Respir Med 2010;104:1050-6
33. Babcock HM, Merz LR, Fraser VJ. Is influenza an influenza-like illness? Clinical presentation of influenza in hospitalized patients. Infect Control Hosp Epidemiol 2006;27:266-70
34. Li G, Yilmaz M, Kojicic M, et al. Outcome of critically ill patients with influenza virus infection. J Clin Virol 2009;46:275-8
35. Cooksley CD, Avritscher EB, Bekele BN, et al. Epidemiology and outcomes of serious influenza infections in the cancer population. Cancer 2005;104:618-28
36. McGeer A, Green KA, Plevneshi A, et al; Toronto Invasive Bacterial Diseases Network. Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. Clin Infect Dis 2007;45:1568-75
37. Oliveira EC, Marik PE, Colice G. Influenza pneumonia: a descriptive study. Chest 2001;119:1717-23
38. Dao CN, Kamimoto L, Nowell M, et al. Emerging Infections Program Network: adult hospitalizations for laboratory-positive influenza during the 2005-2006 through 2007-2008 seasons in the United States. J Infect Dis 2010;202:881-8
39. Muller MP, McGeer AJ, Hassan K, et al; Toronto Invasive Bacterial Disease Network. Evaluation of pneumonia severity and acute physiology scores to predict ICU admission and mortality in patients hospitalized for influenza. PLoS One 2010;5:e9563
40. Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. JAMA 2004;292:1333-40
41. Skiest DJ, Kaplan P, Machala T, et al. Clinical manifestations of influenza in HIV-infected individuals. Int J STD AIDS 2001;12:646-50
42. Angelo SJ, Marshall PS, Chrissoheris MP, et al. Clinical characteristics associated with poor outcome in patients acutely infected with influenza A. Conn Med 2004;68:199-205
43. Meier CR, Napalkov PN, Wegmuller Y, et al. Population-based study of incidence, risk factors, clinical complications and drug utilisation associated with influenza in the United Kingdom. Eur J Clin Microbiol Infect Dis 2000;19:834-42
44. Ljungman P, Ward KN, Crooks BN, et al. Respiratory virus infections after stem cell transplantation: a prospective study from the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant 2001;28:479-84
45. Orzeck EA, Shi N, Blumentals WA. Oseltamivir and the risk of influenza-related complications and hospitalizations in patients with diabetes. Clin Ther 2007;29:2246-55
46. Murata Y, Walsh EE, Falsey AR. Pulmonary complications of interpandemic influenza A in hospitalized adults. J Infect Dis 2007;195:1029-37

47. Nichols WG, Guthrie KA, Corey L, et al. Influenza infections after hematopoietic stem cell transplantation: risk factors, mortality, and the effect of antiviral therapy. Clin Infect Dis 2004;39:1300-6
48. Whimbey E, Champlin RE, Couch RB, et al. Community respiratory virus infections among hospitalized adult bone marrow transplant recipients. Clin Infect Dis 1996;22:778-82
49. Whimbey E, Elting LS, Couch RB, et al. Influenza A virus infections among hospitalized adult bone marrow transplant recipients. Bone Marrow Transplant 1994;13:437-40
50. Vilchez RA, McCurry K, Dauber J, et al. Influenza virus infection in adult solid organ transplant recipients. Am J Transplant 2002;2:287-91
51. Kaiser L, Wat C, Mills T, et al. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. Arch Intern Med 2003;163:1667-72
52. Sessa A, Costa B, Bamfi F, et al. The incidence, natural history and associated outcomes of influenza-like illness and clinical influenza in Italy. Fam Pract 2001;18:629-34
53. Martino R, Rámila E, Rabella N, et al. Respiratory virus infections in adults with hematologic malignancies: a prospective study. Clin Infect Dis 2003;36:1-8
54. Centers for Disease Control and Prevention. 20102011 Influenza Season Summary. Available at http://www.cdc.gov/flu/weekly/weeklyarchives2010-2011/10-11summary.htm. [Last accessed 28 November 2012]

